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Accelerated FDA Approval of Investigational New Drugs: Hope for Seriously Ill Patients

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NOTABLE STUDENT WORK

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I. Introduction

In recent years, seriously ill or dying patients have found it increasingly difficult to obtain new drugs. Many would attribute this difficulty to the Kefauver-Harris amendments that Congress adopted in October, 1962.[1] Although designed to provide greater protection to the American public by requiring proof of both safety and efficacy, the 1962 amendments have created an unacceptably large increase in approval time, a decrease in incentive for drug innovation, and a barrier to the acquisition of necessary drugs for seriously ill patients. Although defenders of the current system call the drug approval system "scientifically rigorous," some critics contend that it is "scientifically rigid, unable to react to the prolonged suffering it imposes."[2] In response to the furor that has raged over the so-called "drug lag," the Food and Drug Administration (FDA) has promulgated new regulations to expedite the new drug approval process.[3] This paper focuses on the evolution of the approval process, from the

1. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended at 21 U.S.C. § 355 (Supp. II 1982)). For an excellent discussion of this topic, see *AIDS Drugs: Where Are They?*, 100th Cong., 2d Sess. (1988); *AIDS, Education, Care, and Drug Development: Hearing Before the Comm. on Labor & Human Resources*, 101st Cong., 1st Sess. (1989).

2. *A Flawed Drug System*, L.A. Daily J., Nov. 27, 1986, at 4, col. 1.

3. *Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale; Final Rule*, 52 Fed. Reg. 19,465 (1987) (codified at 21 C.F.R. § 312) [hereinafter *1987 Regulations*]; *Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Debilitating Illnesses*, 53 Fed. Reg. 41,515 (1988) (codified at 21 C.F.R. §§ 312, 314) [hereinafter *1988 Regulations*].

Kefauver-Harris amendments to the recently enacted Investigational New Drug (IND) regulations, taking into account the costs and benefits of accelerated approval.

II. Drug Approval Under the 1962 Amendments

A. The Kefauver-Harris Amendments

Before the passage of the Kefauver-Harris amendments in 1962, each time a new drug was introduced in the market, the FDA had to approve the new drug application.[4] Unless the FDA rejected the new drug within 180 days for failure to be safe for its suggested use, the drug was considered approved.[5] In 1959, Senator Estes Kefauver initiated Congressional hearings to consider whether the current regulation permitted drugs of questionable efficacy to be marketed to an unwary public.[6] Kefauver's proposal to enact a stricter regulation providing for proof-of-efficacy was met with something less than enthusiasm. The thalidomide tragedy of 1961,[7] however, created a public outcry for greater protection from potentially hazardous drugs. Although the Kefauver-Harris amendments did not provide for greater safety but only efficacy, Congress nonetheless enacted the amendments as a response to public pressure.[8]

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4. Federal Food, Drug and Cosmetic Act of 1938, Pub. L. No. 52-717, 52 Stat. 1040 (current version at 21 U.S.C. §§ 301-392 (1988)); Peltzman, *The Benefits and Costs of New Drug Regulation*, in REGULATING NEW DRUGS 114 (R. Landau ed. 1973).

5. Peltzman, *supra* note 4, at 114.

6. Roberts & Bodenheimer, *The Drug Amendments of 1962: The Anatomy of a Regulatory Failure*, 1982 ARIZ. ST. L.J. 581, 584.

7. Thalidomide is a nonbarbituate hypnotic drug discovered in Germany in 1954. After preliminary animal experiments and clinical trials were completed, the West German pharmaceutical company Chemie Grunenthal began marketing the drug in November of 1956 to treat respiratory infections. In October of 1957 the company began wide-spread marketing of the drug as a sedative under the trade name Contergan. The drug was also used to treat minor ailments such as colds, coughs, and influenza. The drug companies distributing thalidomide advertised the drug as completely safe for use by pregnant women, although none of the companies had performed clinical tests on pregnant animals.

In 1959, users of thalidomide reported side effects such as disturbed balance, constipation, hangover, loss of memory, and toxic polyneuritis; however, the companies continued to market the drug as safe and effective, claiming that the side effects were a result of overdosage and overuse. In 1960, Richardson-Merrell, Inc. applied for a permit to market the drug in the United States, but the FDA denied the request. Finally, the companies marketing thalidomide in Europe withdrew the drug from the market on November 27, 1961, after severe fetal deformity was shown to be a side effect of the drug. Pregnant mothers who ingested the drug gave birth to babies with phocomelia (flipper limbs), microtia (abnormal smallness of the ear), and ectromilia (absence of limbs, or parts of limbs). It is estimated that thalidomide caused birth defects in over 10,000 children. H. TEFF & C. MUNRO, THALIDOMIDE: THE LEGAL AFTERMATH xi-5 (1976).

8. Tests for safety involve the evaluation of the toxic effects of the drug, the manner in which the body distributes and degrades the drug, and the side effects of the varying doses of the drug. *AIDS Treatment, Research & Approval: Hearings Before the Senate Comm. on*

The amendments protect the public from fraudulent drugs, but the addition of efficacy requirements have added a major stumbling block for the approval of beneficial new drugs. Drug manufacturers must provide "substantial evidence" of efficacy based on "adequate and well-controlled investigations" before the drug can be approved.[9] Critics of this standard believe that it is too subjective. Words such as "substantial" and "adequate" are open to varying interpretations.[10]

With the passage of the Kefauver-Harris amendments, the FDA began to take a more active role in the new drug approval process. No longer allowing the forces of the marketplace to control the introduction of new drugs, the 1962 amendments ushered in an era of "centralized regulatory authority."[11]

B. The Drug Approval Process

The drug development process generally begins with animal testing.[12] If a drug appears promising, the manufacturer tests the safety and efficacy of the drug in animals for approximately two years.[13] If the drug passes these tests, the manufacturer files an investigational new drug application with the FDA, which then reviews all the available data.[14] When the FDA gives its approval to continue testing, the manufacturer begins three phases of human testing.[15]

During Phase I, the drug is administered to ten to fifty patients to test how well the patients tolerate, metabolize, and excrete the

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Labor and Human Resources, 100th Cong., 2d Sess. 70 (1988) [hereinafter *AIDS Treatment*]. Efficacy involves the evaluation of the effectiveness of the drug for a particular indication. *Id.*

9. 21 U.S.C. § 355(d)(e) (Supp. II 1982).

10. *Oversight—The Food and Drug Administration's Process for Approving New Drugs: Hearings before the Subcomm. on Science, Research and Technology of the House Comm. on Science and Technology*, 96th Cong., 1st Sess. 76 (1979) (statement of William Wardell) [hereinafter *Oversight*]. Other additions to the drug approval process instituted by the 1962 amendments include Investigational New Drug (IND) requirements and the repeal of automatic approval within 60 days. H. GRABOWSKI & J. VERNON, THE REGULATION OF PHARMACEUTICALS: BALANCING THE BENEFITS AND RISKS 4 (1983). An IND must include information adequate to demonstrate that it is safe to test the drug on human subjects, and further must include information regarding drug composition, manufacturing and control data, results of animal testing, training and experience of the investigators, and a plan for clinical investigation. *AIDS Treatment*, *supra* note 8, at 70.

11. H. GRABOWSKI & J. VERNON, *supra* note 10, at 4.

12. *Id.* at 22.

13. *Id.*

14. *Id.*

15. *Id.* Although these phases are not statutory requirements, they constitute the normal process of drug development. *See generally 1988 Regulations*, *supra* note 3, at 41,518.

drug.[16] The primary focus of this phase is safety.[17] If the drug appears to be safe for human use, Phase II begins.[18] During this phase, fifty to two hundred patients take part in controlled trials, one-half of them generally receiving placebos.[19] At this point, the drug is evaluated from a "therapeutic and marketing standpoint."[20] If the safety and efficacy results of Phase II testing are encouraging, the manufacturer moves to Phase III, and uses over two hundred patients to confirm and expand the results of the first two phases.[21]

After the manufacturer collects sufficient data on the safety and efficacy of the drug, the data is submitted in a New Drug Approval application (NDA) to the FDA for its review.[22] The FDA has 180 days to either approve or disapprove the NDA, but may extend the period to gather further data if the NDA is incomplete.[23] The drug will only be approved if the sponsor of the NDA shows by "substantial evidence" that the drug is safe and effective for the conditions prescribed or suggested on the labeling.[24] A drug manufacturer may choose to engage in post-marketing surveillance, sometimes called Phase IV, although this phase is not required to obtain drug approval.[25]

The period of the approval process, from the synthesis of the New Chemical Entity (NCE) to the eventual approval of the drug, is approximately nine to thirteen years.[26] According to Dr. William Wardell, a well-known critic of the slow drug approval process, average approval time in 1964 was six and one-half years and had

16. *1988 Regulations, supra* note 3, at 41, 518.

17. *Id.*

18. *Id.*

19. *Id.* The second phase concentrates on both safety and efficacy. *1988 Regulation, supra* note 3, at 41,518.

20. H. GRABOWSKI & J. VERNON, *supra* note 10, at 22.

21. *Id.* According to Frank E. Young, Commissioner of the FDA, after Phase I, only 70% of the IND's survive. Of that 70%, only 33% survive Phase II. Of the remaining IND's, only 27% survive Phase III. The reasons for failure include not only lack of safety and efficacy, but also lack of commercial interest. *AIDS Issues: Pending AIDS Legislation: Hearings before the Subcomm. on Health and the Environment of the House Comm. on Energy and Commerce*, 100th Cong., 1st & 2d Sess. 278 (1988) [hereinafter *AIDS Issues*].

22. *AIDS Treatment, supra* note 8, at 71.

23. H. GRABOWSKI & J. VERNON, *supra* note 10, at 23.

24. 21 U.S.C. § 355(d)(e) (Supp. II 1982); *The Food and Drug Administration's Process for Approving New Drugs: Subcomm. on Science, Research and Technology*, 96th Cong., 2d Sess. 17 (1980) [hereinafter *FDA's Process*].

25. *1988 Regulations, supra* note 3, at 41,518.

26. H. GRABOWSKI & J. VERNON, *supra* note 10, at 22; *Commission on the Federal Drug Approval Process: Final Report Prepared by Subcomm. on Natural Resources, Agricultural Research and Environment and Subcomm. on Investigation and Oversight on Science and Technology*, 97th Cong., 2d Sess. 2 (1982) [hereinafter *Commission*].

doubled by 1980.[27] A significant amount of time is involved in the approval process, and arguably too much time.

III. The Role of the FDA

Recently, the FDA has been criticized for its overly cautious approach in approving new drugs. The process has become increasingly lengthy, expensive, and complex. As a result, there has been a rapid decline in the number of new drugs that have been introduced into the market.[28] Patients in desperate need of therapeutic drugs are unable to obtain them for long periods of time. According to the Commission on the Federal Drug Approval Process (Commission), "Regulatory demands and delays within the U.S. drug review system are significant factors" in this delay.[29]

The Commission has suggested a decrease in regulatory burdens in order to make new drugs that are identifiable therapeutic advances more readily available to the public.[30] In order to understand the Commission's proposal, some background on the effects of the 1962 amendments on drug approval is necessary, as is an explanation of the costs and benefits of facilitating the drug approval process.

A. The Drug Lag

During the 1970s, drug manufacturers showed increasing dissatisfaction with the procedure the Food and Drug Administration (FDA) used in approving new drugs. Although at first the FDA denied the existence of a "drug lag,"[31] it soon became clear that the United States greatly lagged behind European countries in the approval of NCE's. New drugs are generally available in the European market either exclusively or much earlier, or for a wider range of

27. *Commission, supra* note 26, at 18 (statement of William Wardell).

28. *Id.* at 1.

29. *Commission, supra* note 26, at 18.

30. With the advent of Acquired Immune Deficiency Syndrome (AIDS), the demand for these new drugs has increased, and the FDA has attempted to meet these demands. *AIDS Treatment, supra* note 8, at 66. In response to the growing AIDS epidemic, Congress enacted the *AIDS Amendments of 1988*, Pub. L. No. 100-607, 102 Stat. 3062-3111 (codified as amended in scattered sections of 42 U.S.C.). Among other things, the Act expedites the award of research grants and the approval of IND's for AIDS. While this effort to ease restrictions on the use of investigational new drugs for AIDS patients is laudable, it must be remembered that AIDS patients comprise only a segment of the group of individuals who are victims of serious or life-threatening illnesses. The concerns of these individuals also need to be addressed.

31. *Commission, supra* note 26, at 21. "Drug lag" is a term used by critics of the FDA drug approval process to connote the delay between the discovery of a drug and the ultimate approval and marketing of that drug.

conditions.[32]

An example of the slow approval time in the United States is the case of the drug Sodium Valproate.[33] First approved in France in 1967, Sodium Valproate was approved and received phenomenal acceptance in at least forty countries before the FDA approved it in 1978.[34] Although other nations consider this drug to be the greatest advance in the treatment of epilepsy in forty years, the FDA classifies it as a modest therapeutic gain.[35] According to Dr. Richard Masland, a more rapid approval of Sodium Valproate would have prevented one million seizures per year and would have saved over $100,000,000 per year in decreased disability payments and increased earning capacity.[36] Several explanations have been offered as to why the United States lags behind other countries in its approval process.

1. The Kefauver-Harris Amendments.—Increased regulation since the passage of the 1962 amendments has been the focal point of blame concerning the drug lag. According to Dr. Wardell, "The greatest cause of delay . . . is the demand of additional proof of efficacy long after scientists would be satisfied that a drug is effective by the data generated."[37] Drug manufacturers must go through a lengthy process in order to acquire the requisite "substantial evidence" of efficacy. These requirements delay FDA approval by at least two to four years.[38] Further, the establishment of regulatory controls over clinical testing has added a significant amount of time to the approval process.

Most important, however, is the increase in public and congressional attention that accompanied the passage of the 1962 amendments. As a result of close scrutiny, the FDA has developed a tendency to restrict the introduction of new drugs. It might be helpful

32. *Oversight, supra* note 10, at 57 (statement of William Wardell). For example, the following drugs for cardiovascular disease were approved in Europe long before they were approved in the United States: propanolol (Inderal), metoprolol (Lopressor), prazosin hydrochloride (Minipress), Minoxidil (Loniten), Ethacrymic Acid (Edecrin), Furosemide (Lasix), and Disopyramide (Norpace). Drugs for neurological diseases (e.g. Depakene, Tegretol, Clonopin), for respiratory diseases (e.g. Bricanyl), for gastrointestinal diseases (e.g. Tagamet), and for a variety of other diseases were available abroad from months to years before they were obtainable in the United States. *Id.* at 36-52.

33. The trade name for Sodium Valproate is Depakene. *FDA's Process, supra* note 24, at 42.

34. *Id.*

35. *Id.*

36. *Id.* at 43.

37. *Oversight, supra* note 10, at 56.

38. Roberts & Bodenheimer, *supra* note 6, at 589.

to examine this effect in terms of a "standard statistical decision-making framework."[39]

In deciding to approve a drug, the FDA may make two types of correct decisions and two types of errors.[40] The correct decisions are to accept drugs that are safe and effective and to reject drugs that are not. The errors are to reject safe and effective drugs (Type 1 error) or to accept drugs that are not (Type 2 error).[41] If an FDA official commits a Type 1 error, drug manufacturers and patients will bear the costs of being unable to procure approval of effective drugs.[42] The rejection of effective drugs will bring little or no comment from a Congressional oversight committee and the media.[43] However, if a Type 2 error is committed, the FDA, and specifically the approving official, will bear heavy costs.[44] Not only will lawsuits ensue and the marketplace destabilize, but, more important, the FDA will fall into disrepute.[45] The agency will be subject to public criticism, and will have to answer to the oversight committee.[46] As former FDA Commissioner Alexander Schmidt described the problem:

> [I]n all of FDA's history, I am unable to find a single instance where a congressional committee investigated the disapproval of a new drug. But, the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them. The message to the FDA staff could not be clearer. Whenever a controversy over a new drug is resolved by its approval, the Agency and the individuals involved will likely be investigated. Whenever such a drug is disapproved, no inquiry will be made. The Congressional pressure for our negative action on new drug applications is, therefore, intense.[47]

The major effect of FDA regulation is not to bar altogether the introduction of new drugs to the market, but to delay considerably that introduction in order to avoid criticism. This delay may increase the probability of the effectiveness and safety of new drugs, but it also prevents ill patients from obtaining new therapeutic drugs.

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39. H. GRABOWSKI & J. VERNON, *supra* note 10, at 9.
40. *Id.* at 10.
41. *Id.*
42. *Id.*
43. *Id.* With the exception of, perhaps, new drugs for AIDS or cancer.
44. H. GRABOWSKI & J. VERNON, *supra* note 10, at 10. The thalidomide tragedy is a good example of a Type 2 error. *Id.*
45. *Id.*
46. *Id.*
47. Grabowski, *The Impact of Regulation on Innovation*, 34 FOOD DRUG COSM. L.J. 555, 558 (1979).

2. The "Knowledge or Research Depletion" Hypothesis.—An alternate explanation of decreasing innovation and increasing unavailability of new drugs is that major drug innovations occur in cycles and that we are currently on a research plateau.[48] A further proposition states that the supply of basic biomedical knowledge has been exhausted, and thus no new therapeutic advances can be made.[49] No empirical proof exists for this hypothesis, but it is a convenient explanation of the drug lag for those who wish to maintain the status quo.[50]

3. The Regulatory Failure Hypothesis.—In addition to increased regulation, the method in which the FDA operates has been cause for concern.[51] The following are operating procedures of the Agency which lead to increased approval time:

> 1. The FDA's attitude is adversarial to sponsors, which is in stark contrast to the more cooperative attitudes shared by the government and industries in technologically advanced countries in Europe.[52]
>
> 2. Internal management problems include:[53]
>
> a) Slow communications with drug manufacturers.[54]
>
> b) Scientific and professional disagreements between the FDA and manufacturers which are not readily resolved and are costly and time consuming.[55]
>
> c) Poor management of human resources.[56]
>
> d) Inefficient use of computerized information systems.[57]
>
> 3. The FDA requires additional testing when foreign data is used, which means that research is duplicated.[58] Because of the time lag between foreign and domestic approval, the FDA often has been accused of using European postmarketing experience as a test for approval.[59]
>
> 4. The FDA requires a defined research plan for clinical

48. *Oversight, supra* note 10, at 73.
49. H. GRABOWSKI & J. VERNON, *supra* note 10, at 35.
50. *Id.*
51. *FDA's Process, supra* note 24, at 59.
52. *Id.*
53. *Id.*
54. *Id.*
55. *Id.*
56. *Id.* at 61.
57. *Id.* at 62.
58. S. FREDMAN, FORBIDDEN CURES 207 (1976); Roberts & Bodenheimer, *supra* note 6, at 590.
59. *FDA's Process, supra* note 24, at 33.

> testing, but the nature of clinical research entails shifts in the direction of plans.[60] Because every change needs to be approved, considerable delay is common.

The above explanations are not mutually exclusive, but all contribute to the growing drug lag in the United States. Most of the blame, however, has fallen on the 1962 amendments. Although it is now settled that there is a drug lag, there is much debate as to its solution.

B. Cost-Benefit Analysis

Experts who are in favor of a shorter approval period argue that the faster approval process in Europe is not a result of lower standards.[61] According to Dr. Lewis Engman, President of the Pharmaceutical Manufacturer's Association (PMA), there is no evidence that the shorter approval times of other countries have resulted in health hazards.[62] To the contrary, the lengthy approval period in the United States for important new drugs fails to provide identifiable safety benefits and deprives the public of therapeutic drugs.[63] Although the goal of drug regulation is to protect public health and safety, the public is not well served if it is denied access to useful medication.[64] Although some benefits of conservative regulation do exist, the costs of delay clearly outweigh them.

1. Costs of Delay.—The costs of delay in the introduction of new drugs may be measured in terms of both human suffering and economics. As mentioned earlier, the delay in marketing Sodium Valproate resulted in one million unnecessary epileptic seizures and a loss of over $100,000,000 in disability benefits and lost wages for every year marketing was delayed.[65] Another example of the cost of delay involves a drug called Oculinum,[66] which was invented approximately ten years ago by Dr. Alan Scott. Oculinum purported to alleviate the symptoms of a debilitating disease called blepharospasm, which consists of severe constant muscular spasms which contort the face and lead to functional blindness.[67] In November of 1986 ap-

60. *Id.* at 54.
61. *Id.* at 31-32.
62. *Id.* at 32 (statement of Lewis Engman).
63. *Id.* at 31.
64. *Commission, supra* note 26, at 1.
65. *See supra* note 21.
66. *A Flawed Drug System, supra* note 2, at 4, col. 1.
67. *Id.*

proval of Oculinum was not forthcoming, leaving the victims of blepharospasm with no remedy for their disease.[68]

Perhaps the most costly delays involve drugs for victims of life-threatening diseases such as cancer and AIDS. To deprive these patients of new drugs when alternative treatments do not exist clearly presents an ethical problem. Patients may sometimes obtain treatment or compassionate use of investigational new drugs. Approval for use, however, is both expensive and time consuming. In addition, the patient must meet stringent qualifications.[69] For example, in 1985, the FDA approved isoprinosine for compassionate use for AIDS victims. The cost of complying with the regulations exceeded $2000 per patient, precluding the manufacturer from making the drug available.[70] It is worth noting that a year's supply of isoprinosine can be bought from the same manufacturer's subsidiary in Mexico for $300.[71] Furthermore, in January of 1987, only a few hundred of the estimated 28,000 AIDS victims had been accepted in FDA-approved studies, most of which utilized placebos.[72] Emphasizing the need for an expedient drug approval process for AIDS patients, one writer noted, "At present mortality rates, a two month regulatory delay in the development of an effective AIDS cure could cost 1,000 lives."[73] As a result of the unavailability of drugs, many patients and physicians are forced to smuggle in the drugs from foreign countries or to obtain them from the black market.[74]

A further cost of delay is the adverse effect on drug innovation.[75] The average cost of introducing a new drug has skyrocketed and the long gestation period has shortened the effective patent life of new drugs.[76] Due to increased regulation, "key personnel" must concentrate on freeing the NDA from delays rather than applying their talents to the discovery of new drugs.[77] As a result of these roadblocks, the incentive to produce NCE's is rapidly declining.

2. Benefits of Delay.—The benefits of the delay of drug approval are obvious: If a manufacturer does not release a new drug to

68. *Id.*
69. Gieringer, *Twice Wrong on AIDS: FDA Frustrates Victims*, L.A. Daily J., Jan. 15, 1987, at 4, col. 3.
70. *Id.* at col. 4.
71. *Id.*
72. *Id.* at col. 3.
73. *Id.* at col. 4.
74. *A Flawed Drug System, supra* note 2, at 4, col. 2.
75. *See generally* Grabowski, *supra* note 47.
76. *Oversight, supra* note 10, at 74.
77. *Id.* at 336 (statement of W. Clarke Wescoe).

the public until extensive testing can be completed, the United States may experience a "death lag."[78] In other words, the United States may observe the postmarketing experience of foreign countries and avoid deaths in this country by refusing to approve drugs that caused serious side effects in foreign countries. One example is the thalidomide incident. By delaying the introduction of thalidomide in the U.S. and by observing the drug's effect in Europe, the FDA prevented the tragedy from occurring in the United States.[79] In addition, delaying the introduction of new drugs gives manufacturers additional time to test adverse drug interactions, and permits physicians to become better acquainted with drugs already on the market.[80]

3. Cost-benefit Analysis.—While the American public has benefited from the delay of the introduction of some drugs, the costs far outweigh the benefits. In minimizing the risk of approval of dangerous drugs, the FDA is precluding the development and approval of beneficial drugs. Although the FDA is attempting to create a "risk-free" drug approval process, the "basic tenet to pharmacology is that to every drug there is a risk."[81] In weighing the benefits against the risks, several critics of the slow drug approval process have noted that the occurrence of side effects, even serious ones, are acceptable when the drug may help a large number of people.

For example, Dr. William Wardell estimates that the drug practolol, if approved in the United States, might cause approximately 1,240 cases of visual impairment and intestinal disorders every year.[82] On the other hand, the drug could prevent 10,000 to 20,000 deaths from secondary myocardial infarction every year.[83] In comparing the number of lives saved to the number of adverse reactions of practolol, the benefits of the drug far outweigh its dangers. As Dr. William Regelson stated, "The loss of countless lives cannot be justified by the argument that a few people's lives are at risk."[84] The FDA believes that delaying the introduction of drugs into the market will reduce risks to the public. In reality, however, it is merely shifting the risk to those patients who could have been helped by the forbidden drugs.

78. Roberts & Bodenheimer, *supra* note 6, at 600.
79. *See supra* note 7.
80. *Id.*
81. *Oversight, supra* note 10, at 335 (statement of W. Clarke Wescoe).
82. Roberts & Bodenheimer, *supra* note 6, at 601.
83. *FDA's Process, supra* note 24, at 32.
84. *Id.* at 36.

After extensive consideration of the above cost-benefit analysis, in 1983, the FDA proposed procedures to make investigational new drugs available to seriously ill patients before general marketing.[85] The proposals were neglected for several years until it was announced that the FDA was reproposing the regulations.[86]

IV. Expediting the Drug Approval Process

In 1987, the FDA reproposed a measure to "ease restrictions on the use and sale of experimental drugs."[87] During Congressional hearings on the reproposal, Dr. Frank E. Young, Commissioner of the FDA, urged Congress to "be flexible [and] recognize that we need new measures in desperate times. We simply cannot be content with business as usual when there is a need to treat desperately ill people."[88] Although the reproposal was intended to expedite approval, it has not succeeded in meeting the FDA's goals. Consequently, in October of 1988, the FDA supplemented the reproposal with new regulations intended to bolster the new drug approval process.[89]

A. The Reproposal of 1987

On March 19, 1987, the FDA issued regulations for drug approval procedures that were "intended to facilitate the availability of promising new drugs to patients as early in the drug development process as possible."[90] According to Dr. Regelson, there are two types of patients who require medical care: those with self-limited or curative problems where treatment is directed toward comfort and shortening of the illness; and those with severe, permanent, debilitating or lethal diseases.[91] The new regulations apply to the latter group of patients.

The FDA bifurcated the category of illness that includes patients with severe, permanent, debilitating, or lethal diseases into "immediately life-threatening" diseases—which would include, for example, AIDS and certain uncontrollable cardiac arrhyth-

85. Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale, 21 C.F.R. §§ 312.7(d), 312.34 (1990).

86. *1988 Regulations, supra* note 3, at 41,516.

87. *FDA Proposals to Ease Restrictions on the Use and Sale of Experimental Drugs: Hearings before the Subcomm. on Human Resources and Intergovernmental Relations*, 100th Cong., 1st Sess. 74 (1987) [hereinafter *FDA Proposals*].

88. *Id.*

89. *1987 Regulations, supra* note 3.

90. *Id.* at 19,466.

91. *Oversight, supra* note 10, at 252.

mias—and "serious" or "severely debilitating" diseases—which would include Alzheimer's disease and multiple sclerosis.[92] In order to obtain treatment under these regulations, the patient must have no "comparable or satisfactory alternative drug or other therapy" available.[93] The new regulations also provide for the sale of investigational new drug products.[94] By allowing the sale of these drugs under specific conditions, the FDA has recognized the necessity of providing incentives to drug manufacturers to develop NCE's.

More significant, however, is the FDA's recognition of the benefits of speedy approval for seriously ill patients. According to the Surgeon General, by 1991 at least 179,000 Americans will have died from AIDS.[95] In response to this life-threatening disease, the FDA approved the immune booster zidovudine (formerly called AZT) in record time.[96] Generally, the drug approval process lasts a minimum of seven years, but for zidovudine the process from clinical trial to approval took only twenty-two months.[97] By foregoing Phase III of the drug approval process, the FDA was able to approve the drug in just 107 days.[98] On March 19, 1987, the day the FDA approved zidovudine, the FDA published the regulations to codify the approval process.[99]

1. Treatment Use of an Investigational New Drug.—Section 312.34 of the new regulations[100] permits a more liberal use of IND's than has heretofore been allowed. The section allows patients who are suffering from life-threatening or other serious diseases to use a drug that is not approved for general marketing provided that no

92. *1987 Regulations, supra* note 3, at 19,467.

93. *Id.* at 19,468.

94. *Id.* at 19,467.

95. *FDA Proposals, supra* note 87, at 78.

96. *AIDS Issues, supra* note 21, at 278.

97. *Id.* at 78, 113. The FDA has made efforts to expedite AIDS drug approvals. A special classification, "1-AA," has been established for all AIDS drugs in order to give these drugs the highest priority in the drug approval process. *AIDS Issues, supra* note 21, at 278. Zidovudine, an inhibitor of the in vitro replication of the AIDS virus, was the first drug reviewed and approved under the new classification. *Id.* at 284, 305. As of February 1, 1988, of 179 applications for approval to test 120 new AIDS drugs, 154 applications were approved for human testing. *Id.* at 285.

Additionally, on February 16, 1988, the FDA announced approval of a treatment IND for the experimental drug trimetrexate to treat Pneumocystis Carinii Pneumonia, a potentially life-threatening lung infection found in 80% of all AIDS patients at some time during the course of the disease. *Id.* at 311, 316. The approval of the treatment IND means that hundreds of AIDS patients will have access to the drug. *Id.* at 311.

98. *FDA Proposals, supra* note 87, at 78, 113.

99. 21 C.F.R. § 312.34.

100. *1988 Regulations, supra* note 3.

effective alternative drug or therapy is available.[101] Under this regulation, life-threatening is defined as a disease in which there is a reasonable likelihood that death will occur in a few months.[102]

The availability of drugs for treatment use varies depending upon the category of disease. For serious diseases, treatment use of drugs may begin only after Phase II investigations, which test efficacy and safety of the drugs.[103] For life-threatening diseases, however, use of a new drug may begin during Phase II.[104] By allowing the use of a new drug before all testing for efficacy and safety is complete, the FDA recognizes that for some individuals, any drug that offers hope is better than no drug at all. As one AIDS patient said, "I know what the side effects of untreated AIDS are. Based on past experience, I'll be dead in two years. What's the harm in giving me some hope?."[105]

In order to obtain an investigational new drug for treatment purposes under a treatment protocol or treatment IND, four criteria must be satisfied:

> (1) The drug is intended to treat a serious or immediately life-threatening disease;
>
> (2) There is no satisfactory alternative drug or other therapy available to treat the disease;
>
> (3) The drug is under investigation in a controlled clinical trial under an effective IND, or the trials have been completed;
>
> (4) The sponsor of the controlled clinical trial is pursuing marketing approval of the investigational drug with due diligence.[106]

In addition, there must be sufficient evidence of the safety and effectiveness of the drug if it will be used to treat serious diseases.[107] An application for use of a drug to treat a life-threatening disease may be denied if clinical data shows no therapeutic benefit or if the drug's benefits are outweighed by unreasonable risk of further illness or injury.[108] These safeguards and the requirements of informed consent, quality control, and due diligence on the part of drug manufacturers in pursuing marketing approval, are designed to protect the

101. 21 C.F.R. § 312.34.
102. *1987 Regulations, supra* note 3, at 19,476.
103. *Id.*
104. *Id.*
105. Gieringer, *supra* note 69, at 4, col. 3.
106. *1987 Regulations, supra* note 3, at 19,476.
107. *Id.* at 19,477.
108. *Id.*

public from fraudulent and dangerous drugs.[109] Though it is not aimed at facilitating availability of drugs for persons with curative diseases, section 312.34 benefits patients with serious and life-threatening diseases by expediting the approval process for treatment purposes.

2. Sale of Investigational New Drugs.—The 1987 regulations provide for the sale of IND's in a clinical trial when such sale will allow the sponsor to undertake or continue clinical trials, but only upon prior written approval from one of several authorities.[110] Because the supply of a test drug is normally a part of the cost of researching and developing the drug, special circumstances must be shown in order to request a sale.[111]

In addition to special sales of IND's, the FDA permits the sale of investigational drugs for treatment use in clinical trials under the following conditions:

> (1) The enrollment in the ongoing clinical trials is adequate;
>
> (2) The sale does not constitute commercial marketing of a new drug for which a marketing application has not been approved;
>
> (3) The drug is not being commercially promoted or advertised;
>
> (4) The sponsor of the drug is actively pursuing clinical studies and marketing approval with due diligence.[112]

The FDA must be notified of the proposed sale, which becomes authorized following thirty days of the FDA's receipt of the application, unless otherwise notified.[113] The FDA retains the power to withdraw authorization of the sale if the price charged is fundamentally unfair.[114] This safeguard prevents sponsors from taking advantage of the more liberal rule, which sponsors might do by engaging in commercial marketing or by extorting money from seriously ill patients who are willing to pay anything for a cure.[115]

By permitting the sale of IND's prior to marketing approval, the FDA addresses a problem like the one faced by Dr. Alan Scott,

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109. *Id.*
110. *Id.* at 19,476.
111. *1987 Regulations, supra* note 3, at 19,476.
112. *Id.*
113. *Id.*
114. *Cf. id.* at 19,467.
115. *Id.*

inventor of Oculinum.[116] Dr. Scott was unable to find a manufacturer for his product, so he manufactured it himself. The FDA, however, would not permit him to sell the drug to cover his expenses. As a result, Dr. Scott was forced to stop making Oculinum. The new regulations obviate such problems by allowing manufacturers to sell IND's so that they can continue to produce those drugs.

As long as manufacturers are permitted to sell their drugs for treatment purposes, they will have a greater incentive to produce them and make them available for treatment use, despite the high cost. The end result is that patients and their physicians benefit as much as the drug manufacturer from the sale of investigational drugs.

3. Criticism of the 1987 Regulations.—Although the regulations speed the drug approval process and include safeguards to protect the integrity of the approval process, neither the proponents of quicker approval nor the proponents of the status quo are satisfied. For example, Martin Robinson, of the Lavender Hill Mob Gay and Lesbian Association, doesn't think the regulations go far enough, and criticizes them as tokenism and public relations.[117] On the other hand, experts in the medical field question the propriety of using drugs not proved to be safe and effective. Dr. Martin S. Hirsch of the Infectious Disease Unit at Massachusetts General Hospital and Harvard Medical School, believes that the release of compassionate IND's will delay the licensure of safe and effective drugs: "Under the rubric of compassion, we would only create false hopes and delay [the] accumulation of accurate knowledge that would save lives."[118] Echoing this sentiment, Dr. Itzhak Brook of the FDA's Anti-Infective Drugs Advisory Committee argues that if drugs are available, patients will not participate in double-blind tests and that future AIDS patients will suffer as a result.[119] Further, the National Institute of Health has expressed concern that an unacceptably high risk-benefit ratio could result if proof of efficacy were no longer required, and that allowing the sale of investigational new drugs could be a disincentive for sponsors to obtain market approval.[120]

During the hearings on the reproposal, Richard M. Cooper, Chief Counsel to the FDA from 1977-1979, suggested a solution to

116. *A Flawed Drug System, supra* note 2, at 4, col. 1.
117. *FDA Proposals, supra* note 87, at 132 (statement of Martin Robinson).
118. *Id.* at 55 (statement of Martin S. Hirsch).
119. *Id.* at 61 (statement of Itzhak Brook).
120. *Id.* at 27, 29.

the problem of proof of efficacy.[121] Instead of requiring proof of efficacy, the FDA could require a rational basis for believing the drug is effective. The final regulations adopted this approach and provided a standard of medical and scientific rationality.[122]

Other suggestions to hasten, yet protect, the drug testing process include replacing the double-blind tests, which are arguably unethical, with historical control studies.[123] Additionally, safeguards within the 1987 regulations are designed to prevent abuse of the regulations by drug manufacturers.

In spite of the criticism of the manner in which the 1987 regulations speed the new drug approval process, the FDA apparently decided that the regulations did not speed the process enough. In October of 1988, the FDA promulgated additional regulations to supplement the 1987 regulations.

B. The Interim Rule of 1988

Encouraged by its success with the expedited approval of zidovudine, the FDA modeled the 1988 regulations after the procedure used to approve zidovudine.[124] An important element of the new regulations is the high level of FDA involvement in the approval process. More important, however, is the early consultation feature, which brings new drug sponsors and FDA officials together early in the drug approval process and could make Phase III obsolete.[125]

Several other modifications of the 1987 regulations are included in the 1988 regulations. For instance, while the 1987 regulations addressed "life-threatening" and "serious" illnesses, the new regulations have replaced "serious" illnesses with "severely debilitating" diseases.[126] In addition, the definitions of "life-threatening" illness and "severely debilitating" diseases have been changed in order to include a wider variety of illnesses.

Although the 1988 regulations purport to provide greater flexibility in statutory interpretation, which creates greater availability of new drugs to a wider variety of people, limitations still are imposed. Only life-threatening and severely debilitating diseases are covered by the regulations, and availability of investigational new drugs for

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121. *Id.* at 7.
122. *1987 Regulations, supra* note 3, at 19,468.
123. *AIDS Drug Development and Related Issues: Hearing before a Subcomm. of the Comm. on Government Operations*, 99th Cong., 2d Sess. 53 (1986).
124. *1988 Regulations, supra* note 3, at 41,517.
125. *Id.* at 41,519.
126. *Id.* at 41,516.

severely debilitating diseases is limited to treatment of morbidity.[127] Even with these limitations, the new regulations are a positive step forward in facilitating access to new drugs for seriously ill patients. The following discussion highlights the features of the 1988 regulations.

1. Early Consultation.—Early consultation between new drug sponsors and FDA officials appears to be the key factor in expediting the drug approval process. Although the 1987 regulations provided for early consultation in the form of a post-Phase II conference, the interim rule has instituted a procedure in which the sponsor of the IND and FDA may meet as early as the period before the submission of the IND.[128] At this meeting, the officials and the sponsor may decide upon the most effective method of animal and early human testing, and may formulate the best method of presenting that data in the IND application.[129] After the Phase I testing has been completed, a further "End-of-Phase-I" meeting may be scheduled at the request of the sponsor in order to choose the format for Phase II that is most suitable for providing adequate data on the safety and efficacy of the particular drug.[130]

The result of this well-controlled procession from animal testing through Phase II should be that safety and efficacy will be proven sufficiently by the end of Phase II, obviating the need for Phase III.[131] When drugs for life-threatening diseases such as AIDS and cancer are involved, mere evidence of safety and efficacy is generally considered sufficient. For example, because the studies for zidovudine were well-controlled, further premarketing studies were not required.[132] Likewise, the benefits of alpha interferons were shown to outweigh the risks in Phase II testing so that the drug could be licensed to treat hairy cell leukemia after Phase II was complete.[133] However, in order to provide sufficient results, these studies must include much larger Phase II tests than were previously required.[134] The more extensive testing in Phase II increases the likelihood that Phase III will be unnecessary.

127. *Id.* at 41,519. Morbidity refers to the disease itself, while symptomatic problems are merely the physical manifestations of the disease, such as pain or fatigue.
128. *Id.* at 41,523.
129. *1988 Regulations, supra* note 3, at 41,523.
130. *Id.*
131. *Id.* at 41,519.
132. *Id.*
133. *Id.*
134. *1988 Regulations, supra* note 3, at 41,521.

Early consultation has been very successful because sponsors do not waste time on unnecessary testing. By collaborating on the most effective method of testing, the sponsors and the FDA avoid the pitfall of poorly designed trials in which drugs are administered without controls and unnecessary animal studies are completed. Further, since the FDA is involved from the beginning of the process, the review of the IND takes considerably less time.

Another change in the drug testing design abolished placebo-controlled studies involving patients with life-threatening diseases when an alternative effective therapy is available.[135] Recognizing the ethical dilemma of withholding therapeutic drugs from dying patients in order to test the new drug, the FDA no longer requires the administration of placebos when an effective drug is available.[136] Instead, the FDA suggests studies comparing patients receiving a known drug with those receiving the new drug alone or the known drug in combination with the new drug.[137] However, when no effective alternative therapy is available, placebo testing is permissible.[138]

Consistent with the 1987 regulations, treatment IND's are available. No changes have been made to that program.

2. Risk-Benefit Analysis.—The interim rule provides for a "medical risk-benefit judgment in making the final decision on approvability."[139] In balancing the risks and the benefits, the FDA will weigh the benefits of the drug, the severity of the disease, and the absence of a satisfactory alternative therapy against the known risks and remaining questions about the drug.[140] Certainly those patients who are terminally ill have little to lose by trying a new drug when no alternative exists, except when the drug might worsen their condition.

Another part of the interim rule permits the FDA to enlist the aid of outside expert scientific consultants or advisory committees in deciding whether to approve the new drug.[141] By seeking the advice of experts, the FDA is attempting to ensure that only safe and effective drugs are ultimately approved for marketing. In addition, the FDA requires replication of key studies, which may be concurrent as long as they are independent, in order to determine the reliability of

135. *Id.* at 41,519.
136. *Id.*
137. *Id.*
138. *Id.*
139. *1988 Regulations, supra* note 3, at 41,523.
140. *Id.*
141. *Id.*

the studies.[142]

3. Phase IV Studies.—The new regulations permit the FDA to require the sponsor to engage in postmarketing surveillance "to delineate additional information about the drug's risks, benefits, and optimal use."[143] By instituting postmarketing surveillance, the FDA is taking into consideration the constructive criticism that it received during the Congressional oversight hearings through the 1970s and early 1980s. Utilizing this procedure expedites the drug approval process, and at the same time, assures safety and effectiveness.

4. Other Elements of the Program.—The 1988 interim rule provides for focused regulatory research on the phases of drug development and evaluation.[144] Also, FDA officials are required to actively monitor clinical trials.

V. Conclusion

Since the passage of the Kefauver-Harris amendments in 1962, critics of the new drug approval process have denounced it as unnecessary and expensive protection against the danger of inefficacious drugs.[145] After many years of research into the drug lag that prevents seriously ill patients from receiving therapeutic drugs for seven to thirteen years after their discovery, the FDA has recognized the urgency of drug approval for the treatment of life-threatening and severely debilitating diseases. Although critics denounce the new procedures, the FDA has taken a courageous step in discharging its duty to protect the health of the public. Approving an expedited drug approval process is courageous; even with safeguards, the risks attendant to new drugs may manifest themselves through adverse side effects in any number of patients. The FDA recognizes, however, that "physicians and patients are generally [more] willing to accept greater risks or side effects from products that treat life-threatening or severely debilitating illnesses, than they would [be to] accept [such risks] from products that treat less serious diseases."[146] Considering the alternatives (death or severe disability), these patients should be permitted to choose a therapeutic drug even though

142. *Id.* at 41,521.
143. *Id.* at 41,524.
144. *1988 Regulations, supra* note 3, at 41,524.
145. MacAvoy, *FDA Regulation-At What Price?*, L.A. Daily J., Nov. 24, 1982, at 4, col. 6.
146. *1988 Regulations, supra* note 3, at 41,516.

it might cause adverse side effects. The loss of a few lives, as weighed against the chance of saving thousands of lives, tips the cost-benefit scale in favor of allowing the new drug.

The future of these facilitated procedures is uncertain. Nevertheless, the alarming spread of the AIDS disease and the elusiveness of any cure for cancer ensures that these procedures will most likely remain effective. Since the new regulations are not applicable to diseases for which there are satisfactory alternative drugs, the general public is not at risk. The safeguards provided by the new regulations should significantly reduce the risks confronted by seriously ill patients.

Considering the narrow scope of the facilitated procedures and the safeguards they provide, it is unlikely that another drug failure catastrophe will occur. In the event that such a disaster does occur, however, the many lives saved versus the few lives lost or persons disabled justifies the use of the expedited procedures. Although the FDA would surely be criticized severely, it has accepted that risk in order to aid those in serious need of aid. The regulations of 1987 and 1988 represent an impressive effort by the FDA to meet the demands of the seriously ill public without compromising safety. The success of the regulations is promising.

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